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ACUTE AND CHRONIC SIDE EFFECTS OF CORTICOSTEROIDS USED FOR TREATMENT OF NEONATAL CONDITIONS

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Review paper

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Summary. Prematurity is a large problem worldwide. Premature infants are at high risk of developing chronic lung disease (CLD). Corticosteroids (CS) have been proven efficient in improving lung function and facilitating weaning of premature infants with CLD from mechanical ventilation. On the other hand, their use has been related to severe short- and long-term side effects. Over the years, CS have been widely used in many conditions in premature infants, but after a connection to severe side effects had been established, their use registered a large downfall, creating the perplexity whether to give CS or not. Clinicians may also be confused in deciding which synthetic CS to use and at what time, dose and duration. A difference in activity and side effects between dexamethasone (DEX) and hydrocortisone (HC) should thereby also be considered. This review describes acute and chronic side effects connected to CS and will attempt to shed light on how clinicians can minimize them.

Introduction

Corticosteroids (CS) have been introduced to perinatal medicine in 1972, when Liggins and Howie published their discovery that prenatal betamethasone administration reduces the incidence of respiratory distress syndrome (RDS)[1]. Postnatally, CS were used in newborns to facilitate weaning from ventilator and in the treatment of adrenal insufficiency and for arterial hypotension.

Nevertheless, recent reports have raised concerns that CS therapy during the perinatal period compromises growth and may cause permanent fetal neurodevelopmental impairment, as well as other acute and chronic complications.

In general, CS stimulates gluconeogenesis and glycogen synthesis and release amino acids from muscles. Glucocorticoids drastically reduce signs of inflammation by modifying leukocyte activity as well as suppressing cytokines, chemokines and other mediators of inflammation. Glucocorticoids inhibit the function of tissue macrophages and other antigen-presenting cells. The production of prostaglandins and leukotrienes is decreased by affecting the expression of cyclooxygenase-2[2]. After a single dose of a short-acting CS, the number of neutrophils increases, whereas the number of monocytes, eosinophils and basophils is decreased. The changes are most evident in the first 6 hours following administration and disappear completely after 24 hours.

Dexamethasone (DEX) has been the most commonly CS used in the prevention and treatment of chronic lung disease (CLD). DEX is a synthetic long-acting CS, with a half-life of 36–54 hours. The alternative is hydrocortisone (HC), which is a short-to-medium-acting CS and is 25–50 times less potent than DEX, with a half-life of 8 hours. Some other synthetic CS used in perinatal medicine are methylprednisolone and budesonide. This review will focus more on intravenous rather than inhaled CS such as budesonide.

Prenatal administration of CS

Prenatal CS is administered with the aim to reduce the incidence of complications and morbidities connected to preterm birth, such as RDS and CLD. Corticosteroids have been shown to have a considerable effect on intrauterine maturation, inducing both structural and functional changes of fetal organs. Structurally, CS increase lung compliance by accelerating alveolarization, enhancing septal thinness and increasing pulmonary collagen and elastin growth. They also affect the fetal lungs by increasing the synthesis of both lipid and protein components of surfactant[3]. Effects of CS are not limited only to the fetal lungs; in the liver, CS increase the synthesis of a variety of proteins and growth factors. This is important in the transition period from fetus to newborn, to ensure the full number of nutritional requirements at birth and in the immediate postnatal period. In addition, CS increase the availability of adrenaline after birth [4]. It has been shown that infants receiving antenatal CS had a significantly lower mortality to discharge when compared to controls[5]. Corticosteroids are recommended for pregnant women from 23 to 33+6 weeks who are at high risk of preterm delivery[6]. Four doses of DEX, of 6 mg for every 12 hours administered intramuscularly are recommended. A synthetic stereoisomer of DEX used for antenatal administration is betamethasone, administered intramuscularly in a 12 mg dose, and another identical dose 18 to 24 hours later.

Betamethasone is favored for this indication due to its reduced attachment to maternal plasma proteins and less biodegradation in the placenta than other CS, therefore delivering a larger fraction of the dose to the fetus[2].

Treatment with antenatal CS is connected to an overall reduction in newborn deaths, intraventricular hemorrhage, and necrotizing enterocolitis, as well as systemic infections[6]. These achievements described more than 45 years ago, have led to widespread use of CS in perinatal medicine. From the early 1990s to 2012, antenatal CS usage increased from 24% to 87%[7].

Side effects of CS used for prevention of RDS in infants

Despite the success in reducing morbidity and mortality in preterm infants, several studies appeared with reports of adverse effects. One study has shown that there is a considerable transient reduction in fetal body and breathing movements and fetal heart rate variation after maternal betamethasone administration[8]. However, it must also be noted that a return of these values to baseline levels was observed on day 4. A retrospective fear must therefore arise, of many unnecessarily induced preterm births upon observation of the findings described above; then considered to be signs of fetal distress, but now suspected only to be a transient consequence of prenatal CS administration. Furthermore, to evaluate the efficacy and safety of prenatally used CS, the dosage was also assessed. Even though data are scarce, many clinicians, to ensure that all newborns who are delivered preterm receive the optimal treatment, often readminister CS when childbirth hasn't occurred in more than 7 days after the first dose. This study, which compared a single-dose application (one course of betamethasone 12 mg applied once in 24 hours) versus weekly doses of antenatal CS (4 courses total, not including the qualifying course) concluded that repeated doses of antenatal CS reduce specific neonatal morbidities, but do not improve composite neonatal outcome. Composite neonatal outcomes in this study included RDS, intraventricular hemorrhage, periventricular leukomalacia, CLD and stillbirth or neonatal death. Furthermore, this is followed by a reduction in birth weight of 95 grams and an increase in number of small for gestational age infants[9]. Even with these findings in mind, there is still no consensus on how exactly to adjust the timing of CS administration and their dosage[10]. To conclude, there is a great amount of evidence that suggests that the use of prenatal steroids in pregnant women who are at risk of a preterm delivery reduces newborn mortality and complications. However, further studies on dosage and choice of prenatal steroids are needed.

Indications for CS in neonatal acute conditions

Corticosteroid treatment is indicated in newborns with congenital adrenal hyperplasia (CAH) and adrenal crisis, 20 to 30 mg/m^2 of HC, divided three times per day. This is a life-saving treatment; therefore, these conditions will not be mentioned in further text. Arterial hypotension is another condition in which CS may be considered. While not the first line of treatment, they should be considered when proper hydration and other drugs do not prove beneficial. In this case, HC is administered in a starting dose of 1–2 mg/kg every 12 hours. When an improvement in blood pressure and urine excretion is observed, the dose can be reduced to 0.5 mg/kg[11].

Indications for CS in chronic neonatal conditions

Corticosteroids are indicated in prolonged mechanical ventilation, with oxygen supplementation, and when there is a high risk of neonatal CLD. This condition of a very preterm infants is caused by persistent inflammation following preterm birth[12]. Well known anti-inflammatory properties of steroids including inhibition of prostaglandins, leukotrienes, and cyclooxygenase I and II, decreased neutrophil recruitment in the lungs, reduction of vascular permeability, and improvement of pulmonary edema, make CS a logical solution for the treatment of CLD. Moreover, CS has a very positive impact on the success of weaning of these patients from mechanical ventilation. These effects are achieved through several mechanisms: surfactant production enhancement, antioxidant properties, bronchospasm decrease, reduction of pulmonary and bronchial edema, improvement of vitamin A status and minimization of inflammatory cells and mediator response[13].

In such occasions the DART (Dexamethasone: A Randomized Trial) protocol can be used. The DART protocol prescribes the administration of intravenous DEX: 0.075 mg/kg per dose every 12 hours for three days, then 0.05 mg/kg per dose every 12 hours for three days, followed by 0.025 mg/kg per dose every 12 hours for two days, and lastly 0.01 mg/kg per dose every 12 hours for two days[14].

Corticosteroids usage in the 1990s rose from 29% in infants who survived more than 12 hours after birth, to 41% in 1996, subsequently falling to 8% and remained relatively stagnant since. Even though postnatal CS usage declined, survival without major morbidity increased 2% every year for newborns of a gestational age from 25 to 28 weeks[7].

The explanation for such a drastic decrease in CS use can be found in several research papers which connected postnatal CS use with severe side effects, both acute and chronic. In Europe, a cohort study has recorded that 13.9% of infants from 24 to 29 weeks of gestational age were treated with postnatal CS. Very extreme variations in CS usage between regions in Europe have been described, ranging from 3.1% to 49.4% infants receiving CS for treatment of CLD[15]. A cohort study, 15-year experience treating extremely low birthweight infants in Australia, showed that even though CS usage fell in

2005 and was accompanied by the rise in CLD, there were no significant changes in mortality or neurological morbidity in comparison to earlier eras when CS were more widely used[16].

Acute side effects

Postnatal CS treatment had been connected to many acute side effects. According to a Cochrane review by Doyle et al.[17], an increased risk of gastrointestinal bleeding and perforation was frequently described in studies focusing on early use of CS (less than 8 days of postnatal age), as well as hyperglycemia, hypertension, hypertrophic cardiomyopathy and growth failure. As for late administration CS, another Cochrane review revealed an increased risk of infection and gastrointestinal bleeding, hyperglycemia, glycosuria and hypertension[18]. From this, we can conclude that short-term side effects can arise regardless of the time of the administration. A study conducted on 220 infants, randomly assigned into two groups – a placebo group and a DEX-treated group with doses of 0.15 mg/kg for 3 days, and then gradually tapered off during the next 7 days, showed that DEX-treated patients were at an increased risk of developing hypertension, hyperglycemia and gastrointestinal perforation[19]. The latter occurred in 13% of treated patients, establishing itself in this study as a particularly dangerous acute CS side effect. Subsequently, its significance has been reaffirmed in other studies and case reports. These show an even greater increase of the risk of gastroduodenal perforation if DEX is given with indomethacin[20,21]. A lowered level of prostaglandins, which usually maintain the integrity of gastrointestinal mucosa, has been proposed as a possible cause of gastrointestinal perforation associated with CS[22]. Decreased weight gain is also one of the side effects appearing in DEX-treated patients[23]. A possible mechanism of growth failure may be related to a catabolic effect of CS, to which very low birth weight infants are more vulnerable. Therefore, in the earliest period of life, when infants naturally receive insufficient calories, their growth may be markedly affected[24]. Another side effect connected to DEX is hypertrophic cardiomyopathy. One study evaluating the effects of early DEX on the heart studied a group of 20 patients receiving placebo and 20 patients who received 0.5 mg/kg DEX per day for 3 days, then 0.25 mg/kg per day for 3 days, then 0.125 mg/kg per day for 7 days, started from fourth day of life, with cardiac evaluations before, during and after the treatment with DEX. This study concluded, that DEX treatment relates to a significant increase in mean septal and left posterior wall thickness, as well as a decrease in mean left ventricle diameter. Twenty percent of infants developed left ventricular hypertrophy; however, complete resolution of hypertrophy was detected within the second and third week following the discontinuation of DEX treatment[25]. Similar results were described in a case report – however, this time only a single dose of 0.5 mg/kg was enough to cause the abovementioned phenomenon[26]. With evidence that DEX has a lot of acute side effects, HC was chosen as the drug of interest for other studies. A case report was published describing cardiac hypertrophy as a consequence of HC treatment, with findings returning to normal after the treatment was terminated[27]. However, it is obvious that larger studies are needed to confirm this side effect of HC. One study concluded, when comparing DEX- and HC-treated patients to their controls, that acute side effects such as hyperglycemia, high urea concentrations, hypertension, and impaired weight gain were connected only to DEX-treated patients in a dose of 0.5 mg/kg tapering off to 0.1 mg/kg for 21 days and not to HC treatment in a dose of 5 mg/kg tapering off to 1 mg/kg for total of 22 days[28]. One randomized clinical trial on a greater number of patients (379) showed that there was no significant difference between HC and controls in acute side effects such as hypertension, hyperglycemia, gastrointestinal perforation and necrotizing enterocolitis. Only late-onset sepsis was found to be more frequent in HC-treated infants from 24–25 weeks of life[29]. On the other hand, there are two studies which were interrupted because of high incidence of spontaneous gastrointestinal perforation, but neither showed a significant increase in other acute side effects. In one of them, 25 patients received 2 mg/kg for 2 day, then 1.5 mg/kg for 2 days, and 0.75 mg/kg for 6 days of HC. A total of 4 of 25 patients developed spontaneous gastrointestinal perforation, three of which received indomethacin or ibuprofen with HC[30]. In the other study, 360 patients were divided into 2 groups, one placebo, and the other the HC group, receiving 1mg/kg per day for 12 days, then 0.5 mg/kg per day for 3 days. The results showed that HC-treated patients who received indomethacin had a higher risk of gastrointestinal perforation than the placebo group also receiving indomethacin, whereas the risk was non-significant when comparing HC-treated infants without indomethacin with controls, also without indomethacin[31]. The studies suggest that combining CS with indomethacin or ibuprofen should be abandoned because of a high risk of gastrointestinal perforation in preterm infants. To conclude, HC in a low dose is not associated with acute side effects, and the elevated risk of gastrointestinal perforation is lowered if indomethacin or ibuprofen are omitted.

Chronic side effects of CS used for the treatment of neonatal conditions

Chronic side effects have been the main reason for the decline in postnatal CS use almost all around the world. The main reason for this decrease is the influx of reports connecting postnatal CS usage to neurodevelopmental side effects such as cerebral palsy (CP). A study on rodents suggested that CS may be the reason for delayed dendritic cortical branching[32]. A follow-up to a randomized, double blinded, placebo-controlled study published in 2000, concluded that DEX was associated with a significant increase in frequency of CP and neu-

rodevelopmental delay[33]. This follow-up included 80 patients which received 0.25 mg/kg DEX every 12 hours for a total of 6 doses in the first three days of life for the prevention of CLD and 79 placebo-treated patients. They were assessed at a mean age of 53 months (range from 24 to 71). DEX-treated patients had a significantly higher incidence of CP (49%) than placebo-treated patients (15%) and developmental delay was also more common in the DEX group (55% vs. 29%). This study raised considerable alarm regarding DEX use in preterm infants, and an urgent need for further studies to determine the dose and timing of CS became apparent. On the other hand, it is known that patients with CLD, as a whole, have a lower average IQ, they have more academic difficulties, behavioral problems and delayed speech and language development at school age[34]. This may suggest that neurodevelopmental difficulties may not be exclusively connected to postnatal CS administration but are also associated to CLD itself. In 2000 Doyle et al[35] performed a meta-analysis of 27 randomized clinical trials studying the effects of CS on mortality and motor function. They concluded that the overall mortality rate was not significantly higher but found that the rate of motor dysfunction was indeed significantly higher in the CS group. One of the studies included in the meta-analysis was conducted on neonates using an early treatment (at less than 4 days postnatal), while four studies considered neonates who were treated later (at more than 14 days postnatal). When excluding the study with early treatment, the rate of motor dysfunction was not statistically significantly higher in the CS group (23% vs. 15%). On the contrary, other three studies showed that CS treatment, even started later, is related to significantly higher rates of CP (22.9% vs. 14.2%). This meta-analysis raised a lot of questions concerning the time of CS treatment, and furthermore showed that CS do not reduce mortality. One study, where 30 neonates, who were oxygen and ventilator dependent on 10th day of life with a high risk of CLD, were divided into 2 groups, with 15 neonates treated with DEX with a total dose of 0.5/mg/kg/day for six days, 0.25/mg/kg/day for another six days, and 0.125 mg/kg/day for two days with a total dose of 4.75 mg/kg over 14 days from the 10th day of life and 15 untreated, were followed up at 36–42 months adjusted postnatal age. In regards to this dose and timing of DEX administration, no significant difference was found in mean body weight and head circumference, as well as the incidence of CP, major neurosensory impairment, mean IQ scores or behavioral abnormalities in neonates at three-year follow up[36]. In 2001 another meta-analysis was performed on 8 randomized control trials that included at least some report of a long-term neurodevelopmental outcome in infants treated with CS for prevention of CLD. These studies were divided into 2 groups regarding the extent of result contamination, defined as CS treatment of controls after the study period. This meta-analysis concluded that the relative risk of CP in a group with less than 30% result contamination was 2.86 and the relative risk for neurodevelopmental disability was 1.66, stating that, without any evidence of long-term benefits, CS should not be used for this indication[37]. Eventually, as a result of collected evidence over the years, American Academy of Pediatrics indeed recommended that routine use of systemic DEX for prevention or treatment of CLD should be abandoned and called for further trials investigating the use of alternative CS, systemic or inhaled[12]. On the one hand, there is evidence that DEX facilitates early extubation and weaning from mechanical ventilation in preterm infants, and it has been proven that low doses (0.89 mg/kg) are also effective over 10 days[14]. On the other hand, a strong connection exists between DEX and CP, especially when DEX is given in high doses during early days of life. Doyle et al[38] set an objective to assess the modification of the effect of CS on CP and mortality, when risk of CLD is taken into account. After 20 randomized control trials had been studied, the authors concluded that if the risk for CLD was below 35%, administration of CS was connected to a significant increase in chance of death or CP. On the other hand, when this risk exceeds 65%, then the chance is decreased. They also reported an increase in CP in early CS therapy, but not in late-administered CS. Nevertheless, even in late use of CS, overall benefits could not be proven. It can be concluded that only patients at a high risk of CLD should receive CS, at the appropriate time and dose, to ensure that the benefit surpasses the risks. In 2009, a nested study was conducted inside a prospective trial on 1667 extremely low birth weight survivors treated late (at more than 7 days postnatal) with CS (94% DEX) and examined at 18–22 months of postmenstrual age. A total of 72% of patients treated with CS were at high risk for CLD. The study concluded that the rise in neurodevelopmental impairment correlated with an increase in dose of CS, where 71% receiving the highest dose achieved a fatal outcome or impairment. For every 1 mg/kg of CS, a 2-point decrease of the mental development index and a 40% increase in risk of CP was remarked. In regards of treatment timing, treating infants at 33 weeks of postmenstrual age was associated with the greatest harm[39]. As was the case with Doyle et al[38], this nested study observed that infants with the highest risk of developing CLD had fewer harmful outcomes. A recent study from 2017 studied 412 infants of a gestational age of 23–28 weeks who were on mechanical ventilation, 29% of which having received DEX (mean cumulative dose was 7.8 mg/kg). The outcomes of interest were respiratory-related hospital admissions in the past 12 months and neurodevelopmental impairment. It was concluded that both early and late DEX groups show a significantly higher frequency of respiratory readmissions (0.35 vs 0.15), a higher incidence of neurodevelopmental impairment, hearing, vision, communication or other disabilities, as well as CP (0.59 vs 0.45)[40]. A Cochrane review of studies on late (after 7 days postnatal) CS treatment, performed in 2017, found no significant difference between CS treatment and controls regarding the combined rate of death, CP, or neurosensory disability. The authors recommended that

late CS therapy should be reserved for neonates who cannot be weaned from mechanical ventilation[18]. Another Cochrane review in 2017 examined studies of early systemic CS therapy (at less than 8 days) for the prevention of CLD and found an increased risk of abnormal findings on neurological examination and an increased risk of CP in these patients. However, the authors also warned that no study had been conducted after the school age or had neurodevelopmental impairment as a primary outcome. Hydrocortisone as well as DEX showed a reduction in rates of patent ductus arteriosus, mortality or CLD, but without evidence of long-term harm[17]. This stressed a greater need for HC trials, as it may be better than DEX for this indication.

Hydrocortisone, to be considered as a possible replacement for DEX, should be as efficient in facilitating weaning from mechanical ventilation and have less side effects. A retrospective study conducted in 2003 investigated the short and long-term benefits of both HC and DEX in two centers. All patients received CS because of impossibility of weaning from the ventilator and had a high risk for CLD. This study showed that HC and DEX are equally potent in reducing oxygen dependency. Most importantly, on late follow-up at 5 to 7 years of age, the group of DEX-treated patients had a significantly increased number of neurodevelopmental disabilities, and more than 50% of them needed special school education. HC-treated patients, on the other hand, showed no difference in neurodevelopmental outcomes in comparison to controls[28]. Another late follow-up study conducted at 8 years of age used magnetic resonance imaging (MRI) and Wechsler Intelligence Scales for Children- Revised (WISC-R) neurocognitive assessments. A reduced volume of grey matter (649 mL vs. 666mL) was found in preterm infants, as well as an increased volume of cerebrospinal fluid (228 mL vs. 206 mL). Total hippocampal volume was decreased (6.1 mL vs. 6.56 mL) and WISC-R score lowered for preterm children (99.4 vs. 109). When comparing HC-treated preterm children to preterm children without HC therapy, there was no significant difference between the two groups in any of the categories mentioned above[41]. There has been a number of other studies which seem to give support to the claim that treatment with HC shows no long term side effects[42,43]. Despite these findings, it was considered that a larger study was required. One such study, conducted in 2007 on a larger number of patients, seemed to confirm previously listed conclusions. A total of 62 patients were treated for CLD with 5 mg/kg/day of HC. This group was compared to 163 controls. Similarly to the studies discussed above, these patients were followed up at 7–8 years old, and again the group that underwent HC treatment showed no significant difference in comparison to controls in regards to motor function (Movement Assessment Battery for Children) and the incidence of CP as well[44]. A Cochrane review recognized the potential of HC in reducing the outcomes of mortality and/or CLD without any long-term harm[17]. Gupta et al[45] concluded in a 2011 that none of the included multicentered RCTs or cohort studies revealed any side effects of neonatal HC treatment on functional or structural neurological outcomes. One retrospective cohort study from 2014 was conducted on 175 extremely low birth weight infants. A total of 86 of them received a maximum daily dose of 3 mg/kg HC per day. The attending physician documented the indication for HC treatment, which were divided according to indication into infants treated with HC for hypotension, respiratory status or other. These infants were neurologically examined at both 8 months and 20 months of corrected age and compared to 89 controls. At 8 months, HC-treated patients were shown to have lower mean motor and fine motor scores. Additionally, the cumulative duration of HC therapy was deemed a negative predictor of language outcomes at 8 months follow-up, as well as of motor outcomes at 20 months[46]. However, on second follow-up at 20 months, language and fine motor skills were observed as having improved. This study warned about the effect of cumulative days of HC exposure on extremely low birth weight infants. Although a lower dose than in other studies was used, it was the duration of HC treatment that was connected to motor abnormalities at 20 months of age. This is not the only study showing neurodevelopmental abnormalities in connection to HC therapy. An example is a follow-up study on a randomized trial of early neonatal HC treatment published in 2016, with the aim of evaluating neurodevelopment and growth of 5 to 7-year-old children treated with HC in the first days since premature birth. All the patients in this study were on mechanical ventilation in the first day of life. This original study was however terminated, because of increased risk for gastrointestinal perforation in the HC group. Eighty percent of children continued to participate in the study at the 5 to 7-year mark. The conclusion in this instance was that neurodevelopmental impairment occurred in a significantly larger percentage within the HC group (61% vs. 39%). HC-treated patients had a lowered mean full-scale IQ (87.8 vs. 95.7) and mean performance IQ (88.3 vs. 99.1); 22% of HC-treated patients had a need for physiotherapy (22% vs 0%) and the need for speech therapy was higher in HC group as well (47% vs. 28%)[47]. These studies indicate that HC should not be used in the first days of life, and not in a longer duration than 40 days. There is a noticeable need for similar studies that aim to pinpoint the ideal duration and timing of HC treatment, but on a larger number of patients. In 2016, for example, a multicenter randomized trial was conducted on extremely preterm infants (<28 weeks of gestation) to assess if low-dose HC therapy improves survival without CLD. Infants were assigned into 2 groups, 266 of which received placebo and 255 infants received 1 mg/kg of HC per day. It was shown that HC significantly improved survival without CLD at 36 weeks of age. Furthermore, HC significantly increased the proportion of extubated infants at the end of the study, reduced the need for surgical ligation of patent ductus arteriosus, and increased the percentage of

infants who do not need supplemental oxygen at 36 weeks[29]. This study used the lowest dose that has so far been proven to increase survival of CLD. Even though HC had been administered from the first day of life, a follow-up study at 2 years of age showed no significant difference in neurodevelopmental impairment[48]. To sum up, so far HC has proved to be as efficient as DEX with less short-term and long-term side effects. A lower dose and shorter duration of HC therapy is generally recommended, but future studies are needed to identify the exact dose and duration, so that clinicians can utilize this treatment without fear of acute or chronic side effects.

Conclusion

Postnatal CS treatment of preterm infants is helpful in terms of weaning from mechanical ventilation and improving lung function. However, these beneficial effects are accompanied by significant acute and chronic side effects. Clinicians need to outweigh the ratio of risk and benefit for each individual infant they treat, keeping in mind that only infants at high risk of CLD are likely to benefit from this treatment. Early administration of DEX should be avoided, while HC arises as a more comfortable choice with less short- and long-term side effects, especially in a low dose. Further studies to determine the appropriate dosage and correct timing of CS may give more insight in the question of postnatal CS treatment in the future.

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AKUTNE I KRONIČNE NUSPOJAVE KORTIKOSTEROIDA U LIJEČENJU NOVOROĐENČADI

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Pregledni članak

Ključne riječi: deksametazon, hidrokortizon, neurorazvoj, novorođenče, nuspojave

Sažetak. Prerano rođena novorođenčad i komplikacije koje se pojavljuju kod njih problem su u cijelome svijetu. Takva djeca su pod velikim rizikom razvijanja kronične plućne bolesti (CLD). S obzirom na upalnu etiologiju CLD-a, kortikosteroidi (CS) su predstavljeni kao logičan izbor liječenja takvog stanja. Oni su se pokazali vrlo učinkovitima u popravljanju plućne funkcije i u ubrzavanju odvajanja djece sa respiratora. Prvi CS korišten za ovu indikaciju je bio deksametazon (DEX) koji se od 1990-tih sve više koristi, do 41% u postnatalno vrijeme, da bi se do danas smanjio na 8%. Razlog tom drastičnom padu uporabe CS-a leži upravo u povezanosti sa akutnim i kroničnim nuspojavama. Uz akutne nuspojave, otkrilo se da CS-i mogu biti povezani s cerebralnom paralizom (CP) u nedonoščadi. S obzirom na to, savjetuje se da se DEX koristi u situacijama kada je novorođenče i nakon 2 do 3 tjedna i dalje mehanički ventilirano i kada postoji izraziti rizik od razvoja CLD-a, i to u što manjoj dozi. Hidrokortizon (HC) je još jedan sintetski CS, koji svojim mogućnostima odgovara kortizolu, istraživan je kao moguća zamjena DEX-u. Dokazi su pokazali da HC ima jednako dobar učinak u novorođenčadi u prevenciji CLD-a i u odvajanju od mehaničke ventilacije kao i DEX. Hidrokortizon nije bio značajno povezan s akutnim nuspojavama kao DEX, osim s povećanom učestalošću spontane intestinalne perforacije u kombinaciji s indometacinom ili ibuprofenom. U studijama koje su pratile djecu tretiranu HC-om kroz 7–8 godina, HC nije bio statistički povezan sa većom učestalošću neuroloških nuspojava ni CP-e. Samo je par studija uočilo neurorazvojne probleme uz liječenje HC-om, no te studije su ili koristile HC rano nakon rođenja u većim dozama ili tijekom dužeg razdoblja (>37 dana). Zaključno, postnatalni CS su korisni u odvajanju od respiratora i u poboljšanju plućne funkcije u nedonoščadi. Međutim, ovi dobri učinci su popraćeni akutnim i kroničnim nuspojavama. Kliničari bi trebali za svakog pojedinog pacijenta odvagnuti koristi i rizike, tako da samo ona novorođenčad koja imaju veliki rizik za razvoj CLD-a budu liječeni CS-ma.